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A randomized study of tiotropium Respimat® Soft Mist™ Inhaler vs. ipratropium pMDI in COPD

T. Voshaar[a], R. Lapidus[b], R. Maleki-Yazdi[c], W. Timmer[d], E. Rubin[e,*], L. Lowe[f], E. Bateman[g]

[a]*Medizinische Klinik III, Stiftung Krankenhaus Bethanien für die, Grafschaft Moers, Bethanienstr. 21, D-47441 Moers, Germany*
[b]*Rocky Mountain Center for Clinical Research, 8550 West 38th Ave., #202 Wheat Ridge, CO 80033, USA*
[c]*Respiratory Diseases and Critical Care Medicine, 984 Bay Street, Suite 501, Toronto, Ont., Canada M5S 2A5*
[d]*A Klinische Forschung, Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorferstr. 65, Postfach 1755, 88397 Biberaach/Riβ, Germany*
[e]*Respiratory, Clinical Operations, Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, Ridgefield, CT 06877, USA*
[f]*Clinical Research Strategy, Medical Division, Boehringer Ingelheim Ltd., Ellesfield Avenue, Bracknell, Berkshire RG12 8YS, UK*
[g]*UCT Lung Institute, George Street, Mowbray, Cape Town 7700, South Africa*

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KEYWORDS
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Summary
The aim of these studies was to compare the efficacy and the safety of tiotropium, delivered via Respimat® Soft Mist™ Inhaler (SMI), a novel multi-dose, propellant-free inhaler, with ipratropium pressurized metered-dose inhaler (pMDI) in chronic obstructive pulmonary disease (COPD) patients.

Two identical, 12-week, multi-national, randomized, double-blind, double-dummy, parallel-group, active- and placebo-controlled studies were performed. COPD patients were randomized to treatment with either inhaled tiotropium (5 or 10 μg) via Respimat® SMI administered once daily, ipratropium (36 μg) pMDI QID or placebo. The primary endpoint was the mean trough forced expiratory volume in 1 s (FEV_1) response after 12 weeks of treatment. Secondary endpoints included other spirometry measures and rescue medication use.

A total of 719 patients were randomized; the majority were male (69%) with a mean pre-bronchodilator FEV_1 (% predicted) of 40.7%. The mean treatment differences between tiotropium 5 and 10 μg and placebo for the primary endpoint (mean trough FEV_1 response at week 12) were 0.118 and 0.149 L, respectively (both $P<0.0001$). Treatment differences between tiotropium 5 and 10 μg and ipratropium were 0.064 L ($P=0.006$) and 0.095 L ($P<0.0001$). The increases in peak FEV_1, FEV_1 $AUC_{(0-6\,h)}$ and FVC for both tiotropium doses were statistically superior to placebo ($P<0.01$) and higher than ipratropium. All active

*Corresponding author. Tel.: +1 203 778 7753; fax: +1 203 791 6158.
E-mail address: erubin@rdg.boehringer-ingelheim.com (E. Rubin).

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treatments significantly reduced the rescue medication use compared with placebo, but only tiotropium 10 μg was statistically superior to ipratropium ($P = 0.04$). The incidence of adverse events was comparable across groups.
In conclusion, tiotropium 5 and 10 μg daily, delivered via Respimat® SMI, significantly improved lung function compared with ipratropium pMDI and placebo.

Introduction

The anticholinergics, tiotropium and ipratropium, are established options for first-line maintenance therapy for the treatment of chronic obstructive pulmonary disease (COPD).[1–3] Ipratropium, however, has a short (i.e., ⩽6-h) duration of action, making repeated daily dosing necessary. In contrast, tiotropium has a prolonged muscarinic M_3 receptor blockade, leading to sustained 24-h efficacy with once-daily dosing.[3,4] Tiotropium has demonstrated superiority over salmeterol in several measures including forced expiratory volume in 1 s (FEV_1) after 6 months of treatment.[5,6] In addition, it has been shown to improve health status and dyspnoea, and to reduce exacerbations and hospitalizations compared with placebo and ipratropium.[3,7] More recently, tiotropium has been demonstrated to improve exercise endurance, and to decrease hyperinflation in patients with COPD.[8–10]

In all these studies, tiotropium was administered via the HandiHaler®, which is a dry-powder, breath-actuated inhaler.[11] More recently, an alternative propellant-free, multi-dose inhaler (Respimat® Soft Mist™ Inhaler [SMI]) has been developed, which uses mechanical energy from a spring, rather than inspiratory flow, to generate a fine, low-velocity mist. Compared with pressurized metered-dose inhalers (pMDIs), the fine particle fraction (<5.8 μm) from Respimat® SMI is approximately 2.5 times greater, the velocity about five times slower, and the duration for dose release is about seven times longer.[12,13] These characteristics increase lung-drug deposition, reduce oropharyngeal deposition and simplify the co-ordination of actuation and inhalation with Respimat® SMI.[14–17] The relative ease of use of Respimat® SMI, and patient preference over pMDIs and dry-powder inhalers (DPIs), has been demonstrated in several studies.[18–20]

The aim of the current studies was to compare the efficacy and the safety of two doses of tiotropium delivered once daily via Respimat® SMI with placebo and ipratropium pMDI administered four times daily in the treatment of patients with COPD.

Methods

Study design

Two identical, 12-week, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel-group studies were conducted in 39 centres across Germany, Italy, South Africa and Switzerland (#205.251) and in 25 centres across the USA and Canada (#205.252). The studies were designed to compare the efficacy and the safety of two once-daily inhaled doses of tiotropium (5 and 10 μg, delivered via SPIRIVA® Respimat® SMI) (Boehringer Ingelheim, Ingelheim am Rhein, Germany) with inhaled ipratropium bromide (36 μg, delivered via pMDI) and placebo (delivered via Respimat® SMI and pMDI) in patients with moderate-to-severe COPD. The double-dummy feature prevented both investigators and patients from differentiating active drug from placebo, despite the different inhaler devices, which could otherwise not be blinded. Both studies included a 3-week follow-up period. The studies took place from November 2002 to December 2003, and were conducted according to the requirements of good clinical practice and other international and local regulations. The protocols were approved by independent ethics committees. The subjects were given comprehensive verbal and written information about the objectives and possible risks involved in participation in the study. All patients provided written, informed consent to participate. The studies were sponsored by Boehringer Ingelheim and Pfizer.

Participants

Males and females aged ⩾40 years with a diagnosis of COPD, moderate-to-severe airway obstruction with a pre-bronchodilator FEV_1 of ⩽60% of predicted normal, FEV_1/forced vital capacity (FVC) ⩽70%,(based on ECCS values[21]) and a smoking history of ⩾10 pack-years were included. Patients were excluded if they had a history of asthma, allergic rhinitis, any other significant respiratory illness or if they had a condition that could influence their ability to participate in the study. Other exclusion criteria included known hypersensitivity to anticholinergics, prior use of tiotropium, regular use of daytime oxygen therapy, significant alcohol or drug abuse or participation in another study. Pregnant or nursing women, or women of childbearing potential not using contraception, were also excluded.

Medication restrictions

Rescue medication (salbutamol pMDI) was permitted as needed during the study. Oral corticosteroids (equivalent of <10 mg prednisone per day), orally inhaled corticosteroids, theophyllines and mucolytics were allowed if stabilized for at least 6 weeks prior to and throughout the study. Oral β-adrenergics and other investigational drugs were not allowed for at least 1 month prior to run-in. Cromolyn sodium and nedocromil sodium were not allowed for at least 3 months prior to run-in. Anticholinergics, inhaled β-adrenergics other than salbutamol or fixed combination inhalers were also not allowed during the treatment period.

Interventions

Following screening (Visit 1) and a 2-week run-in period, eligible patients were randomized (Visit 2) to tiotropium, ipratropium or placebo. Tiotropium was administered once daily and ipratropium/placebo were delivered four times daily. Tiotropium (5 μg [two actuations of 2.5 μg] or 10 μg [two actuations of 5 μg]) was delivered via Respimat® SMI once daily in the morning with two inhalations of placebo pMDI. A further two inhalations of placebo pMDI were taken at midday, early evening and before bedtime to achieve blinding. Ipratropium (36 μg [two actuations of 18 μg]) was delivered via pMDI in the morning, together with two inhalations of placebo Respimat® SMI. A further two inhalations of ipratropium pMDI were taken at midday, early evening and before bedtime. For the placebo, two inhalations of placebo Respimat® SMI and two inhalations of placebo pMDI were taken in the morning. A further two inhalations of placebo pMDI were taken at midday, early evening and before bedtime. Both the investigator and the patient were blinded to the randomization process. All medications were self-administered by the patient.

Assessments

The primary endpoint was the change in trough (i.e., morning pre-dose) FEV_1 after 12 weeks of treatment. Secondary spirometry endpoints included FVC, peak expiratory flow rate (PEFR) and the number of patients achieving a 15% increase above baseline (i.e., pre-dose on test Day 1) in FEV_1. Spirometry measures were performed in accordance with American Thoracic Society criteria[22] at 10 ($\pm$5) min pre-dose and up to 6-h post-dose. PEFR was recorded in patient diary cards. Other secondary endpoints included the weekly mean number of occasions per day that rescue medication (salbutamol) was used; the severity of COPD symptoms (i.e., wheezing, shortness of breath, coughing and tightness of chest), which was based on the physician's assessment of the patient's condition during the week prior to a clinic visit, and was rated from 0 (not present) to 3 (severe); the physician's global evaluation of the patient's condition, which was rated on an 8-point scale from poor (1–2) to excellent (7–8). Safety was assessed by adverse events, vital signs, 12-lead electrocardiograms (ECG), routine laboratory tests and physical examination.

Statistical analysis

The protocol stated that the statistical analyses were to be performed both for the individual studies and on the combined data from the two studies. Efficacy was to be established in each study. This paper describes the combined analysis. The primary analysis was a step-wise procedure that sequentially tested each tiotropium dose, first for superiority vs. placebo, then for non-inferiority vs. ipratropium and (assuming the initial tests were successful) for superiority vs. ipratropium (a total of six hypothesis tests). An analysis of covariance (ANCOVA), which used terms for smoking status, treatment and centre, and baseline as a linear covariate, was performed for the primary endpoint, secondary spirometry endpoints, physician's global evaluation and COPD symptom scores. Separate ANCOVA models were fitted for each timepoint and test day. Descriptive statistics were used for safety variables. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 8.0 and classified by system organ class and preferred terms. All randomized patients with any available data were included in the safety evaluation, and all those with baseline data and at least one adequate measurement of trough lung function parameters following $\geqslant$5 days of randomized treatment were included in the efficacy analysis (full analysis set).

Results

Patient characteristics

A total of 361 and 358 patients were randomized to treatment in trials #205.251 and #205.252, respectively. The patient characteristics at baseline are shown in Table 1. Patients were comparable across treatment groups; overall, 69% were male, with a mean age of 64 years (standard deviation [SD] 9) and 97% were white. The mean duration of COPD was 10 years (SD 8) and the mean smoking history was 51 pack-years (SD 29). The pooled mean FEV_1, FVC and PEFR were similar across treatment groups, and a significant proportion of patients (46%) were global initiative for chronic obstructive lung disease (GOLD) stage II (i.e., 50% $\leqslant$post-bronchodilator $FEV_1 < 80\%$). Mean baseline rescue salbutamol use, which was assessed during the run-in period, was also comparable between-treatment groups. A total of 87 patients (12%) discontinued prematurely (16 in the tiotropium 5 μg group, 18 in the tiotropium 10 μg group, 31 in the ipratropium group and 22 on placebo).

Primary endpoint

Compared with placebo, there was an increase in trough FEV_1 after treatment with tiotropium 5 and 10 μg (Table 2). "Steady state" was achieved in the first week of therapy for the tiotropium 5 μg dose, and the improvement in both the tiotropium groups was sustained after 12 weeks of treatment. The increase in trough FEV_1 at week 12 in both the tiotropium groups was statistically superior to that observed with placebo (both $P < 0.0001$), and was statistically superior compared with ipratropium 36 μg ($P < 0.01$). The improvement in FEV_1 after 1 week was sustained at 12 weeks of treatment.

Secondary endpoints

The pooled mean FEV_1 response, measured pre-dose (trough) up to 6-h post-dose is shown in Figure 1 for test Days 1 and 85. The secondary spirometry endpoints are summarized in Table 3. The increases in peak FEV_1, FEV_1 $AUC_{(0-6\,h)}$, trough FVC, peak FVC and FVC $AUC_{(0-6\,h)}$ at week 12 for both tiotropium doses (5 and 10 μg) were all statistically superior to placebo, and both the doses of tiotropium were numerically higher than ipratropium for these measures; this difference reached statistical

Table 1 Patients demographics* and pulmonary function test results by treatment group for all randomized patients at screening.

Variables†	Tiotropium 5 μg Respimat® ($n = 180$)	Tiotropium 10 μg Respimat® ($n = 180$)	Ipratropium 36 μg pMDI ($n = 178$)	Placebo ($n = 181$)
Male (%)	69	72	67	69
Age (years)	64 (9)	64 (9)	65 (8)	63 (9)
Current smoker (%)	37	37	40	43
Smoking history (pack-years)	52 (30)	53 (31)	48 (25)	51 (30)
Duration of COPD (years)	10 (8)	10 (9)	10 (7)	9 (7)
FEV_1 (L)	1.10 (0.42)	1.14 (0.41)	1.16 (0.43)	1.20 (0.40)
FVC (L)	2.40 (0.83)	2.46 (0.81)	2.43 (0.83)	2.53 (0.81)
FEV_1 (% predicted)	40 (12)	39 (12)	41 (13)	42 (12)
FEV_1/FVC (%)	47 (11)	47 (11)	48 (11)	48 (11)
PEFR (morning) (L/min)‡	221 (78)	238 (87)	236 (90)	241 (82)
Rescue salbutamol use (occasions per day)‡	2.9 (2.5)	3.0 (2.7)	2.9 (2.6)	2.4 (2.4)
GOLD stage (%)§				
⩾80%	<1	0	0	< 1
50–<80%	41	42	49	52
30–<50%	47	44	39	37
<30%	12	13	11	10
Patients (%) *taking pulmonary medication* (>25%)				
Inhaled corticosteroids	48	51	50	52
β-Agonists, long acting	39	44	43	40
β-Agonists, short acting	69	67	69	64
Anticholinergics, short acting	48	46	47	45

pMDI, pressurized metered-dose inhaler; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEFR, peak expiratory flow rate; GOLD, global initiative for chronic obstructive lung disease.

*Patients were comparable across treatment groups.

†Mean (SD) unless otherwise stated.

‡$n = 683$.

§Post-bronchodilator FEV_1 expressed as % of predicted.

Table 2 Treatment differences for mean trough FEV_1 (L) response at week 12 ($n = 689$).

Treatment difference	Treatment comparisons			
	Tiotropium 5 μg–placebo	Tiotropium 10 μg–placebo	Tiotropium 5 μg–ipratropium 36 μg	Tiotropium 10 μg–ipratropium 36 μg
Mean (SE) [95% CI]	0.118** (0.023) [0.072, 0.164]	0.149** (0.023) [0.103, 0.195]	0.064* (0.023) [0.018, 0.110]	0.095** (0.023) [0.050, 0.141]

FEV_1, forced expiratory volume in 1 s; SE, standard error; CI, confidence interval.*$P<0.01$; **$P<0.0001$.

significance for FVC $AUC_{(0–6\,h)}$ and trough FVC (tiotropium 10 μg dose only). These findings support those observed for the primary variable. The weekly morning (trough) and evening PEFR were both higher for the tiotropium groups than either placebo or ipratropium over the 12-week treatment period (Figure 2). The between-treatment differences at week 12 were statistically significant, showing that both the doses of tiotropium were superior to placebo and ipratropium (largest: $P<0.001$) (Table 3).

The number of responders (⩾15% increase in FEV_1 above test Day 1 pre-dose) within 2 h of dosing is shown in Figure 3. A higher proportion of patients in the ipratropium group achieved a 15% increase during test Day 1 compared with either tiotropium or placebo; however, after 12 weeks of

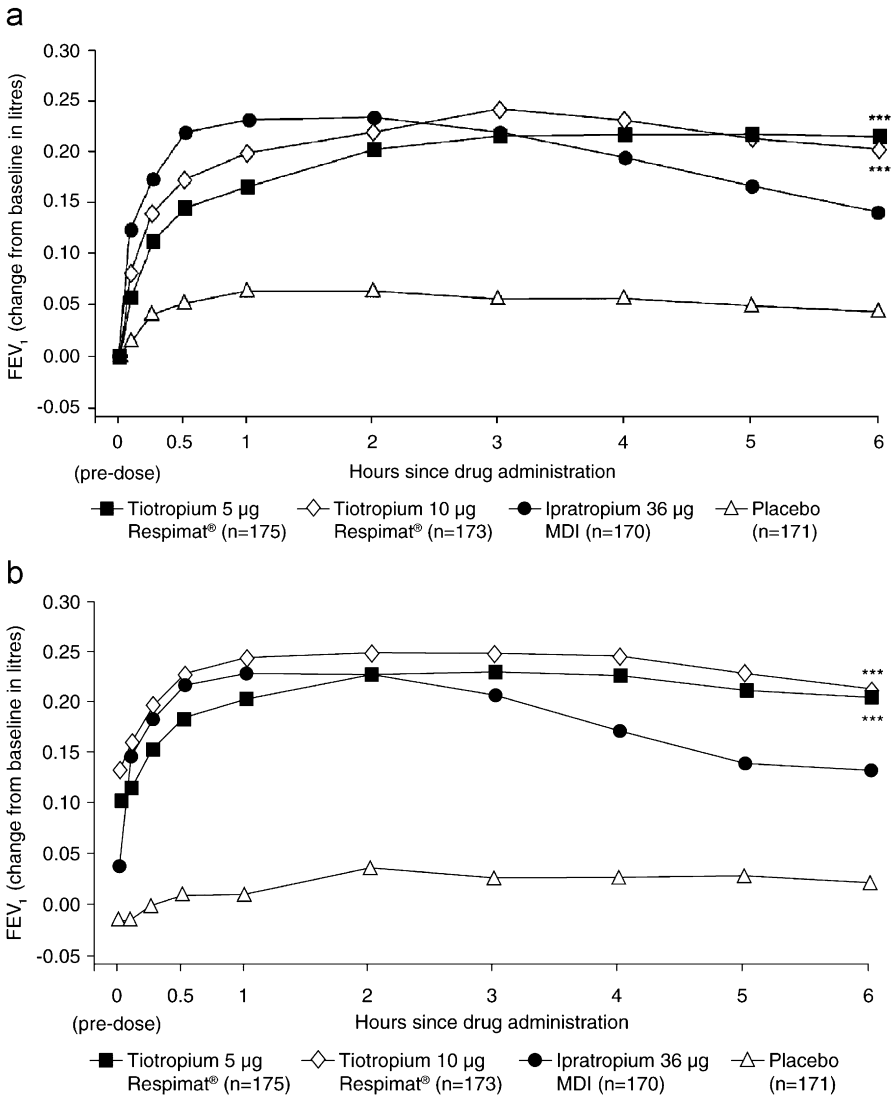

Figure 1 The mean FEV_1 (L) response up to 6-h post-dose following treatment with tiotropium 5 µg Respimat® SMI ($n = 175$), tiotropium 10 µg Respimat® SMI ($n = 173$), ipratropium 36 µg pMDI ($n = 170$) or placebo ($n = 171$). Data are expressed as change from baseline on Day 1 (a) and after 12 weeks of treatment (b). FEV_1, forced expiratory volume in 1 s; ***$P < 0.0001$ tiotropium–placebo. Note: Missing data were imputed by carrying either the lowest or last value forward depending on why the data were missing. Means were adjusted for smoking status, investigational centre and baseline FEV_1 using ANCOVA. A separate ANCOVA was fitted for each time point and test day.

treatment the number of responders in the three active treatments was comparable: tiotropium 5 µg (70%), tiotropium 10 µg (72%), ipratropium 36 µg (69%).

All three active treatments reduced the rescue medication use throughout the 12-week study period compared with placebo (Figure 4). The between-treatment differences showed statistical superiority over placebo for tiotropium 5 µg ($P = 0.0061$) and tiotropium 10 µg ($P < 0.0001$), but only tiotropium 10 µg was statistically superior to ipratropium ($P = 0.04$).

At week 12, the scores for the COPD symptoms "wheezing" and "tightness of chest" were statistically significantly lower for tiotropium 5 µg ($P < 0.05$ vs. placebo) and tiotropium 10 µg ($P < 0.05$ vs. placebo), and the "tightness of chest" score was significantly lower for tiotropium 5 µg than ipratropium ($P = 0.0021$) and for tiotropium 10 µg than ipratropium ($P = 0.0141$). There were little differences between active treatments for "shortness of breath" or "coughing" after 12 weeks of treatment. Both the tiotropium doses significantly improved physician's global evaluation score on each test day compared with placebo ($P \leqslant 0.02$); however, ipratropium showed minor improvements compared with placebo. During the 3-week follow-up period, there was no evidence of a rebound effect following the cessation of treatment. At 3-week post-treatment, the mean number of occasions of rescue medication use was −0.5 to −0.6 per 24 h on active treatment and −0.2 per 24 h on placebo, and, at 3-week post-treatment, the morning PEFR (L/min) was also higher on Respimat® SMI 5 and 10 µg (23 and 20 L/min) compared with ipratropium (11 L/min) and placebo (13 L/min).

Table 3 Treatment differences for pooled secondary spirometry endpoints at week 12 ($n = 689$).

Treatment difference, mean (SE)	Treatment comparisons			
	Tiotropium 5 μg–placebo	Tiotropium 10 μg–placebo	Tiotropium 5 μg–ipratropium 36 μg	Tiotropium 10 μg–ipratropium 36 μg
FEV_1 $AUC_{(0–6\,h)}$	0.191*** (0.025)	0.214*** (0.025)	0.025 (0.025)	0.048 (0.025)
[95% CI]	[0.142, 0.241]	[0.164, 0.264]	[−0.024, 0.075]	[−0.001, 0.098]
FEV_1 $peak_{(0–6\,h)}$	0.193*** (0.028)	0.229*** (0.028)	0.012 (0.028)	0.048 (0.028)
[95% CI]	[0.138, 0.248]	[0.173, 0.284]	[−0.042, 0.067]	[−0.007, 0.103]
Trough FVC (L)	0.132* (0.046)	0.180*** (0.046)	0.077 (0.046)	0.125* (0.046)
[95% CI]	[0.041, 0.223]	[0.089, 0.271]	[−0.014, 0.168]	[0.036, 0.216]
Morning PEFR (L/min)	25*** (5)	23*** (5)	24*** (5)	21*** (5)
[95% CI]	[15, 36]	[12, 33]	[13, 34]	[11, 32]
Evening PEFR (L/min)	32*** (6)	29*** (6)	22*** (6)	19** (6)
[95% CI]	[21, 43]	[18, 40]	[11, 33]	[8, 30]

SE, standard error; FEV_1, forced expiratory volume in 1 s; AUC, area under the curve; CI, confidence interval; FVC, forced vital capacity; PEFR, peak expiratory flow rate.*$P<0.01$; **$P<0.001$; ***$P<0.0001$.

Safety assessments

The total incidence of adverse events was comparable across treatment groups (Table 4). ''Respiratory, thoracic and mediastinal disorders'' were the most frequently reported MedDRA system organ class of adverse events across all groups. Gastrointestinal disorders were more common in the active treatment than placebo groups. Both the tiotropium groups were associated with a higher incidence of dry mouth than ipratropium or placebo: tiotropium 5 μg (8.9%), tiotropium 10 μg (10%), ipratropium (4.5%) and placebo (2.2%). There were no withdrawals due to dry mouth. The percentage of patients who discontinued due to an adverse event was lower in the tiotropium groups than in the ipratropium group: tiotropium 5 μg (7.2%), tiotropium 10 μg (6.7%), ipratropium (11.8%) and placebo (8.8%). Unexpected worsening of COPD was the most common reason for discontinuation: tiotropium 5 μg (3.3%), tiotropium 10 μg (1.7%), ipratropium (6.2%) and placebo (6.1%). The number of patients who experienced serious adverse events was low: tiotropium 5 μg (0.6%), tiotropium 10 μg (1.4%), ipratropium (2.4%) and placebo (0.7%). Two deaths occurred in the tiotropium 10 μg group, which were due to exacerbation of COPD with respiratory failure and cardiac arrest, and one pancreatic cancer-related death occurred in the ipratropium group. There were no clinically relevant changes in the vital signs, the physical examinations and 12-lead ECG throughout the studies.

Discussion

The aim of this active- and placebo-controlled combined analysis was to determine the efficacy and the safety of tiotropium, delivered via Respimat® SMI, compared with ipratropium administered using a pMDI. The pooled analysis showed that once-daily tiotropium (5 and 10 μg) significantly increased 12-week trough FEV_1, the primary endpoint, compared with ipratropium pMDI administered four times daily and placebo. Trough FEV_1 is an important measure, since it represents the minimum improvement experienced by the patient during the course of the dosing period and, for tiotropium, indicates the effects a full day after the preceding dose. Overall, the number of clinically relevant therapeutic responders after 12 weeks of treatment was comparable with all active treatments. These findings show that full efficacy (i.e., ''steady-state'') improvements with tiotropium, delivered via Respimat® SMI, were achieved in the first week of the treatment, and were sustained after 12 weeks of the treatment, with no evidence of the development of tolerance.

Both tiotropium 5 and 10 μg also improved the secondary spirometry measures, compared with both placebo and ipratropium. The sustained improvement in FVC observed with tiotropium has important potential benefits as it is frequently associated with reductions in hyperinflation and symptoms associated with the latter.[3,7,9,23] In addition, significant improvements in COPD symptom scores for wheezing and tightness of chest were observed for both the doses of tiotropium, compared with placebo. Tiotropium also reduced the need for rescue medication compared with placebo and ipratropium. This may be related to the sustained improvement in lung function seen with tiotropium compared with ipratropium. Despite its more rapid onset of action, ipratropium has a considerably shorter duration of effect, as seen in the 6-h post-dose profiles of FEV_1 performed at weeks 1 and 12. This would also explain the lower morning (trough) PEFR values compared with both the doses of tiotropium.

The results observed in this study, in which tiotropium was delivered via Respimat® SMI, are generally comparable to previous studies using the HandiHaler®.[24] In a 1-year trial with the latter, the mean increase in trough and peak FEV_1 relative to placebo was 150 and 220 mL, respectively,[7] and, in two trials, improvements compared with placebo and ipratropium on outcomes such as exacerbations, hospitalizations and heath-related quality of life over a 12-month treatment period were statistically superior.[3,7] Given that the spirometric and other results obtained with tiotropium

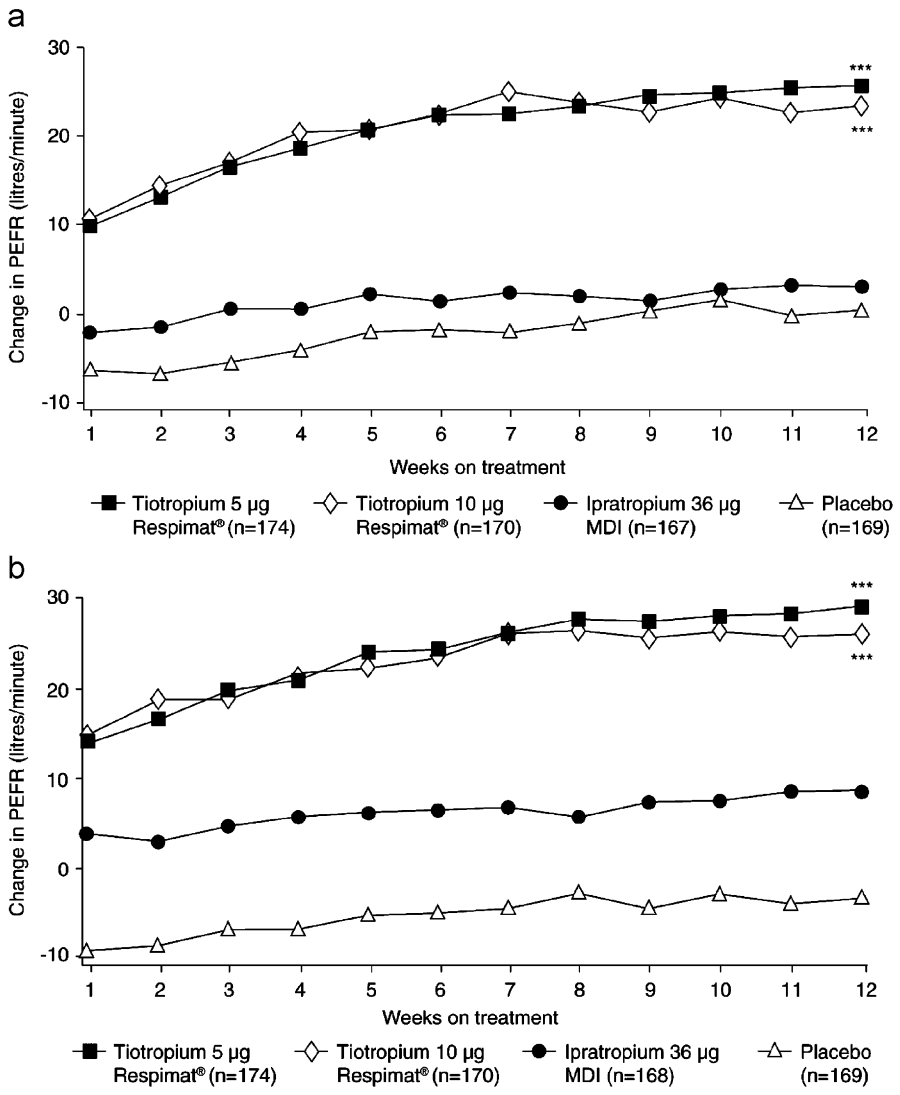

Figure 2 The weekly mean change in PEFR (L/min) following treatment with tiotropium 5 µg Respimat® SMI ($n = 174$), tiotropium 10 µg Respimat® SMI ($n = 170$), ipratropium 36 µg pMDI ($n = 167$–168) or placebo ($n = 169$). Morning PEFR data are shown in (a) and evening PEFR data are shown in (b). PEFR, peak expiratory flow rate; ***$P < 0.0001$ tiotropium–placebo. Note: Missing data were imputed by carrying either the lowest or last value forward depending on why the data were missing. Means were adjusted for smoking status, investigational centre and baseline morning PEFR using ANCOVA. A separate ANCOVA was fitted for each week.

in the current trial were similar to those seen with the HandiHaler®, similar effects on other health-related outcomes may be anticipated, but must be examined in further studies.

Although tiotropium is well established as COPD maintenance therapy when used with the HandiHaler® device, these results support its use with a new device, Respimat® SMI. Two randomized studies that compared tiotropium delivery via HandiHaler® or Respimat® SMI in COPD patients have been completed.[25] A pooled analysis showed that after 4 weeks of treatment, the mean trough FEV_1 was statistically significantly higher (~30 mL) following treatment with tiotropium 5 and 10 µg Respimat® SMI compared with tiotropium 18 µg HandiHaler®. The current analysis shows that Respimat® SMI significantly improved lung function when compared with another first-line therapy, ipratropium pMDI. Overall, these analyses clearly demonstrate the benefits associated with the Respimat® SMI device. However, the current study does have a number of limitations. It is well established that tiotropium can improve inspirational capacity and reduce the operational lung volumes of COPD patients, which correlates with an improvement in dyspnoea and quality of life; however, such measurements were outside the scope of the present studies.

Recent reports suggest that the response to treatment in COPD can be hindered by inhaler technique, and patient satisfaction and adherence.[26] Metered-dose inhalers (MDIs) and DPIs have a number of problems; for example, patients can find it difficult to co-ordinate actuation with inhalation with pMDI devices. Small volume nebulizers (SVNs) are easier to use, but the size of the equipment can be a limitation.[27] Design convergence has enabled the beneficial features of an SVN and an MDI to be combined, which has resulted in the development of Respimat® SMI.[27]

Drug delivery via Respimat® SMI is independent of inspiratory effort and the device is easily portable.

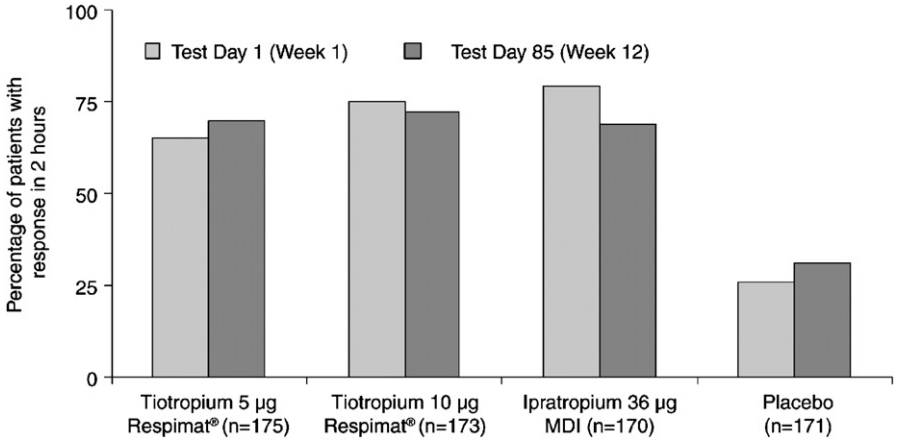

Figure 3 The percentage of responders (defined as a $\geqslant$15% increase in FEV_1 above baseline from 2 h of dosing) following treatment with tiotropium 5 µg Respimat® SMI ($n = 175$), tiotropium 10 µg Respimat® SMI ($n = 173$), ipratropium 36 µg pMDI ($n = 170$) or placebo ($n = 171$). Data are shown on Day 1 and after 12 weeks of treatment. FEV_1, forced expiratory volume in 1 s.

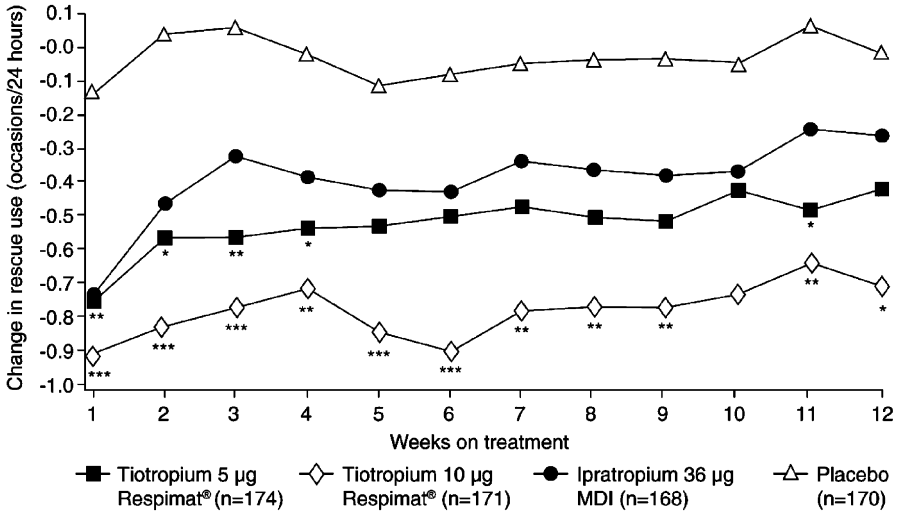

Figure 4 The mean weekly reduction in the rescue medication use following 12 weeks of treatment with tiotropium 5 µg Respimat® SMI ($n = 174$), tiotropium 10 µg Respimat® SMI ($n = 171$), ipratropium 36 µg pMDI ($n = 168$) or placebo ($n = 170$). *$P<0.01$; **$P<0.001$; ***$P<0.0001$—placebo. Note: Missing data were imputed by carrying either the lowest or last value forward depending on why the data were missing. Means were adjusted for smoking status, investigational centre and baseline rescue use using ANCOVA. A separate ANCOVA was fitted for each week.

Table 4 Number (%) of patients with adverse events ($\geqslant$3%) in any treatment group.

Total, *n* (%)	Tiotropium 5 µg Respimat® ($n = 180$)	Tiotropium 10 µg Respimat® ($n = 180$)	Ipratropium 36 µg ($n = 178$)	Placebo ($n = 181$)
Total with any adverse event	95 (52.8)	108 (60.0)	106 (59.6)	107 (59.1)
Diarrhoea	3 (1.7)	4 (2.2)	6 (3.4)	4 (2.2)
Dry mouth	15 (8.3)	18 (10)	7 (3.9)	4 (2.2)
Nausea	0 (0)	3 (1.7)	6 (3.4)	3 (1.7)
Urinary tract infection	9 (5.0)	4 (2.2)	3 (1.7)	4 (2.2)
Headache	6 (3.3)	8 (4.4)	7 (3.9)	13 (7.2)
Bronchitis	8 (4.4)	3 (1.7)	8 (4.5)	7 (3.9)
COPD exacerbations	17 (9.4)	26 (14.4)	24 (13.5)	21 (11.6)
Dyspnoea	4 (2.2)	5 (2.8)	9 (5.1)	9 (5.0)
Pharyngitis	7 (3.9)	8 (4.4)	8 (4.5)	12 (6.6)

Respimat® SMI offers another form of delivery of tiotropium, thus offering the prescribers and the patients a choice. In addition, a patient who has used tiotropium HandiHaler® for a long time may be able to switch to tiotropium Respimat® SMI if needed. Switching could also improve (or alter) deposition, and enable a drug to be used longer without dosing or tolerance issues, although these benefits have not been proven in clinical trials. Furthermore, Respimat® SMI improves the delivery of drug to the lungs.[12–17] In addition, this delivery device allows for a lower inhaled dose with a comparable efficacy to the HandiHaler®.[25]

In published systematic reviews of the DPIs, the MDIs and the nebulizers for delivering inhaled drugs, the devices were found to be equally efficacious (if used correctly) and one of the driving factors for successful therapy was patient preference and adherence.[28] Although Respimat® SMI was not included in these meta-analyses, a recently published randomized controlled trial, in which Berodual Respimat® SMI was compared with Berodual MDI in 245 patients, 81% (162/201) preferred Respimat® SMI.[19] Overall, these discussions suggest that Respimat® SMI could be a valuable addition for use in the COPD maintenance therapy. In the current analysis, the results clearly showed that Respimat® SMI was particularly beneficial in patients with moderate-to-severe airway obstruction. Other studies are underway to explore the benefits of Respimat® SMI in a wider patient population.

The safety profile of tiotropium has been well established. As in the previous clinical studies, dry mouth, attributable to the anticholinergic effect of tiotropium, was the most commonly reported adverse event in the current study, and occurred more frequently than in patients treated with ipratropium and placebo.[3,6,7,23] The similar efficacy and safety results in the current study achieved at a lower dose of tiotropium in the Respimat® SMI compared with the HandiHaler® are consistent with the previous studies confirming superior drug delivery to the lower respiratory tract achieved with the Respimat® SMI.

In conclusion, tiotropium (5 and 10 μg), when delivered via Respimat® SMI, is safe and significantly improves objective lung function compared with placebo and ipratropium, delivered via a pMDI. Respimat® SMI also provides symptomatic benefits.

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Conflict of interest statement

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